# ALUMINUM-MEDIATED ONE-POT CONVERSION OF α-AMINO ACID ESTERS TO THREO 2-AMINO ALCOHOLS WITH HIGH DIASTEREOSELECTIVITY

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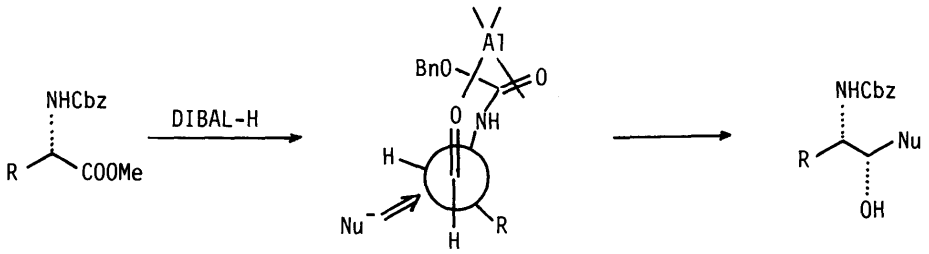
Reduction of N-Cbz α-amino acid esters with DIBAl-H, followed by treatment with Grignard reagent in a one-pot manner gave the corresponding threo 2-amino alcohols with high diastereoselectivity without racemization.

**KEYWORDS** 2-amino alcohol; α-amino acid ester; DIBAL-H reduction; α-amino aldehyde; chelation controll; diastereoselective synthesis; one-pot synthesis

The presence of 2-amino alcohol in biologically active molecules such as amino sugars, antibiotics, and peptides has raised the interest in the diastereoselective synthesis of these compounds.[1] Furthermore, recently, the 2-amino alcohol moiety has been used as the dipeptide isostere in peptidomimetic chemistry.[2] Particular attention has been directed toward the diastereoselective synthesis of 2-amino alcohol by using N-protected chiral α-amino aldehydes.[3] These are of special interest owing to their ready availability from α-amino acids and to their pronounced versatility in organic synthesis.[3] Although an alkylation of chiral α-amino aldehydes is one of the most facile methods to get chiral 2-amino alcohols, the level of the diastereoselectivity is usually low[4] in the alkylation step. Furthermore, chiral α-amino aldehydes are known to be prone to racemization.[3,5] A one-pot conversion of N-Cbz α-amino acid esters to chiral 2-amino alcohols via α-amino aldehyde might effectively avoid racemization. Reduction of α-amino acid esters (DIBAL-H) and the subsequent alkylation (Grignard reagent) procedure was examined in the expectation that high threo selectivity might be expected because of the chelation control in the DIBAL-H reduction intermediates,[6] as depicted in the following Scheme. The results of the studies are described here.

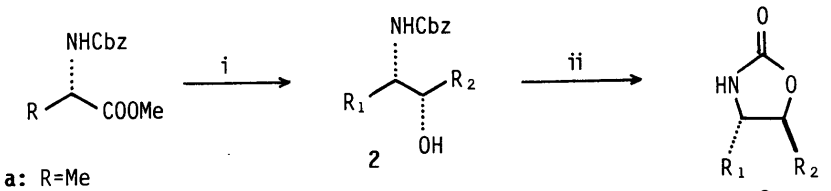



chelation controlled
(Si) attack

Reduction of N-Cbz (S)-alanine methyl ester (**1a**) with DIBAL-H (1.3 eq, ether, -78°C, 1 h), followed by treatment with methylmagnesium bromide, allylmagnesium bromide and phenylmagnesium bromide (ethereal solution, 4 eq, -78°C → room temperature, 2 h) in a one-pot manner gave the corresponding 2-amino alcohols (**2a-c**) in the yields shown in the Table I. Considerably low yields for the products would be, most possibly, caused by the low yield in a DIBAL-H reduction of N-Cbz α-amino acid esters.[3] Since the ratio for threo/erythro of **2a-c** was not determined precisely at this stage, they were treated with base (7.5 N KOH/MeOH/THF; 1:2:4, room temperature, 14 h)[7] until **2a-c** disappeared on thin layer chromatography, and were then made neutral with 10% HCl to avoid ring-opening during the work up to give the correponding (4S,5S)-5-substituted 4-methyloxazolidin-2-ones (**3a**,[7] **3b**,[8] **3c**,[7]), respectively, with considerably high diastereoselectivity in **3a,c**. (See Table 1). The ratio for 4,5-trans/cis-isomer can be easily determined based on the signals due to 4-H and 5-H in their $^1$H-NMR spectra.[7,8] The reason for the comparatively low diastereoselectivty in the formation of **3b** was not clear at this stage. In a similar way, N-Cbz (S)-α-amino acid

methyl esters (**1b,c**) were converted to **3d**,[7] **3e**,[9] **3f**,[8] **3g**,[10] **3h**,[7] **3i**[8] via **2d-i**, respectively, in the yields summarized in the Table I. The ratio for threo/erythro of **2g,h** was also determined by conversion to the corresponding acetates and the results were consistent with those obtained by conversion to **3g,h**. The diastereoselectivity of allylation products (**2e,i**) was also low compared to the other alkylation products. The method for a synthesizing of **2f** from **1b** with high diastereoselectivity in a one-pot manner provides an alternative procedure for the facile synthesis of (3S,4S)-statine (**4**).[9,11]

The remarkably high diastereoselectivity in the formation of 2-amino alcohols can be accounted for by aluminum-mediated chelation control in the alkylation of the α-amino aldehyde intermediates. When N-Cbz (S)-alaninal was treated with ethylmagnesium bromide, the ratio for threo/erythro of **2a** was at most 2.5:1. No racemization during the conversion of **1** to **3** was proved by $^1$H-NMR ($CDCl_3$, 400 MHz) analysis of the Mosher esters (**6a,b** 98% ee) obtained from **5**, derived from **3g** (i. $Boc_2O$, $Et_3N$, DAMP, THF, ii. LiOH-aq. dioxane),[7,9] and (both (+)- and) (-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid.[12] Although yields for 2-amino alcohols are not optimized at this stage, the method described in this paper should be widely applicable to a diastereoselective synthesis of chiral 2-amino alcohols from α-amino acids without racemization.




**1a:** R=Me
**b:** R=i-Bu
**c:** R=$C_6H_5CH_2$

Cbz=$COOCH_2C_6H_5$

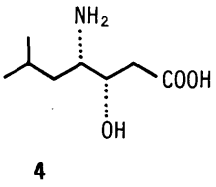
For **2** and **3**

**a:** $R_1$=Me, $R_2$=Et
**b:** $R_1$=Me, $R_2$=$CH_2CH=CH_2$
**c:** $R_1$=Me, $R_2$=$C_6H_5$
**d:** $R_1$=i-Bu, $R_2$=Et
**e:** $R_1$=i-Bu, $R_2$=$CH_2CH=CH_2$
**f:** $R_1$=i-Bu, $R_2$=$C_6H_5CH_2$
**g:** $R_1$=$C_6H_5CH_2$, $R_2$=Me
**h:** $R_1$=$C_6H_5CH_2$, $R_2$=Et
**i:** $R_1$=$C_6H_5CH_2$, $R_2$=$CH_2CH=CH_2$

i. DIBAL-H, -78°C, then $R_2MgBr$, rt. ii. 7.5 N KOH-MeOH-THF (1:2:4), rt.

Table I. 2-Amino Alcohols (**2a-i**) and Oxazolidin-2-ones (**3a-i**) from **1a-c**

| Compound | Yield (%) | Compound | Yield (%) | ratio for trans:cis |
|---|---|---|---|---|
| **2a** | 57 | **3a** | 88 | 9:1 |
| **2b** | 62 | **3b** | 85 | 3.5:1 |
| **2c** | 60 | **3c** | 83 | 7:1 |
| **2d** | 58 | **3d** | 85 | 10:1 |
| **2e** | 58 | **3e** | 83 | 3:1 |
| **2f** | 60 | **3f** | 88 | 11:1 |
| **2g** | 60 | **3g** | 86 | 10:1 |
| **2h** | 62 | **3h** | 88 | 12:1 |
| **2i** | 57 | **3i** | 85 | 3:1 |

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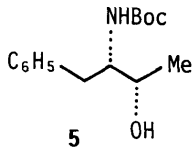
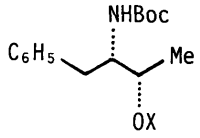
3g → 


5 → 


**6a:** X=(+)-MTPA
**b:** X=(-)-MTPA

Boc=COO-$^{t}$Bu

MTPA=$C_6H_5$-C(OMe)(CF$_3$)-CO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